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# THE ANAPHYLACTIC REACTION WITH SO-CALLED PROTEOSES OF VARIOUS SEEDS

## THE BIOLOGIC REACTIONS OF THE VEGETABLE PROTEINS, VI *

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Altho the toxicity of proteoses and peptones derived from animal tissues has been extensively investigated,[1] their antigenic capacity has received relatively little attention. Few useful conclusions can be drawn from most of this work since it has been done chiefly with Witte's "peptone." As the composition of this commercial product is uncertain, the results which have been reported are of doubtful value. (Zunz states that different samples of Witte's "peptone" may vary in the proportion of proteose nitrogen from 47.52 to 83.21 percent.) Since the literature of this subject has been thoroughly reviewed by Zunz,[2] the results recorded may here be summarized briefly by stating that (1) as far as the precipitin reaction is concerned, negative results have been obtained with peptone and proteose preparations; (2) we can find no statements concerning complement-fixation antibodies for substances of this class; (3) the attempted demonstration of anaphylactogenic properties in proteoses derived from animal proteins has usually given negative results. One of us has studied all the different fractions obtainable from tryptic and peptic digestion of egg-white, both coagulated and raw, and has been unable to find any evidence whatever that its proteoses, peptones, or any of the lower products of hydrolysis, can sensitize guinea-pigs either to egg-white or to the digestion products themselves.[3] Such fragments do not cause intoxication of animals sensitized with egg-white, nor do they prevent reactions in such animals when egg-white is subsequently injected. The supposedly protec-

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[1] See review by Gibson, Philippine Jour. Sc., 1913, 8, p. 475.

[2] Ztschr. f. Immunitätsforsch., 1913, 16, p. 580.

[3] Wells, Jour. Infect. Dis., 1909, 6, p. 506.

tive action, described by Biedl and Kraus,[4] who used Witte's peptone in dogs, was therefore not exhibited. From these observations, and others in which various steps in the enzymatic disintegration of proteins had been studied by the reaction of anaphylaxis, the conclusion was drawn that, as far as anaphylaxis is concerned, nothing less than entire protein molecules can act as antigens.

The only observations to the contrary are those of Zunz and of Abderhalden. Zunz[5] states that he produced both active and passive anaphylaxis in guinea-pigs and rabbits with hetero-albumose, proto-albumose, and synalbumose, but that synalbumose is only able to sensitize. Negative results were obtained with all the other products of proteolysis, including thio-albumose, "secondary proteoses," Siegfried's pepsin-fibrin-peptone β, as well as the lower abiuret products. The hetero-albumose was generally more effective than the proto-albumose. This work has been in part repeated by Friedberger and Joachimoglu,[6] who, using the same preparations of proto-albumose and hetero-albumose that Zunz had employed, found no anaphylactogenic properties in these proteoses: they neither sensitized to serum, nor caused reactions in animals when used for both the intoxicating and sensitizing doses. These authors point out errors in Zunz's work which they believe account for his supposedly positive results.

Abderhalden reports that he has obtained typical anaphylaxis reactions with the fraction of "silk peptone" precipitated with ammonium sulphate, but not with the fractions which this salt failed to precipitate. With a polypeptid containing fourteen radicals of amino-acids (including only glycin and leucin), he[7] observed a fall of temperature, and, in another experiment, a more severe reaction, with convulsions and death (after six hours!). Since the details of this experiment are omitted, a critical consideration is impossible.

In many grains and seeds are found protein substances which, on account of their solubilities, have been designated as "proteoses." As to the immunologic relations of these naturally occurring vegetable proteoses, we have found only the following:

Schloss[8] studied a boy suffering from an urticarial eruption whenever he ate eggs, almonds, or oatmeal. Experiments showed that of the various preparations from almonds and oatmeal, the most active in producing local skin reactions in this subject were the "proteoses" of these seeds, possibly because of their greater solubility.

Schneider[9] found the strong hemagglutinative principle of Phaseolus to be a proteose which disappears during germination.

DeWaele[10] ascribes toxic properties, similar to those of albumoses in general, to a product obtained by heating wheat-gluten with dilute hydrochloric acid.

[4] Wien. klin. Wchnschr., 1909, 22, p. 363.
[5] Ztschr. f. Immunitätsforsch., 1913, 16, p. 580.
[6] Ibid., 1914, 22, p. 522.
[7] Ztschr. f. physiol. Chem., 1912, 81, p. 315.
[8] Amer. Jour. Dis. Child., 1912, 3, p. 341.
[9] Jour. Biol. Chem., 1912, 11, p. 47.
[10] Ztschr. f. Immunitätsforsch., 1912, 13, p. 644.

These few observations on the antigenic power of animal and vegetable proteoses have led us to study the immunologic relations of the so-called proteoses obtained from seeds, and to compare them with proteoses made by artificial methods from the more abundant proteins of some of the same seeds.

Extracts of practically all seeds thus far examined contain a small amount of protein which cannot be separated by prolonged dialysis in water, nor by heating for a long time at 100 C. Since the solubility of this protein corresponds to that of the proteoses produced by the action of proteolytic enzymes on native proteins, they have been called vegetable "proteoses." It is not known that any chemical relation exists between these vegetable "proteoses" and those produced by enzymes, for none of them has ever been obtained in sufficient quantity to make a satisfactory comparison possible. We do not know therefore whether these vegetable "proteoses" have as complex a structure as the native proteins, or a simpler one, corresponding to the proteoses formed from native proteins by hydrolysis. Furthermore, we do not know whether these "proteoses" are original constituents of the seed, or are formed during the processes incident to their separation from the extract. It is probable that enzymatic decomposition of the reserve protein of many seeds takes place during extraction, notably in the case of the flax-seed[11] and lupine-seed,[12] and in such cases preparations of "proteose" from these seeds doubtless consist largely of hydrolytic decomposition products of the reserve protein.

Some seeds contain protein which can be separated by dialysis from the extract only when this is slightly acid, i. e., the greater part of their reserve protein behaves like a globulin when combined with a small proportion of acid, and much like a proteose when free from combined acid, for in this condition it is very imperfectly coagulated by heat. In such cases it is difficult, if not impossible, to separate the reserve protein from the proteose. Examples of such seeds are the almond, hazel-nut, and walnut (*Juglans*).

From these statements it is evident that preparations of the natural vegetable "proteoses" are of uncertain chemical nature, and that they require much more careful study than they have as yet received, before any definite characteristics can be assigned to them.

In order to determine the anaphylactogenic activity of these "proteoses," and their immunologic relations to the reserve proteins of the seeds from which they were obtained, we have made the experiments reported in the following pages. The results described in this paper must be regarded as preliminary to a more precise study, because most of the preparations used were by-products obtained in previous investigations with entirely different objects, and were not sufficiently purified to make them suitable for final experiments of the kind here reported. The results of this preliminary survey furnish a basis for further study, and it is our intention, in the near future, to repeat the experiments here described, using more carefully purified preparations made especially for the work.

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[11] Osborne, Am. Chem. Jour., 1892, 14, p. 629.

[12] Osborne and Harris, Am. Jour. Physiol., 1905, 13, p. 436.

In all cases the injections were made intraperitoneally, and the terms indicating the severity of the reactions have the same significance as in previous articles.[13] The nature and results of these experiments are summarized in the following tables:

TABLE 1

"PROTEOSE," CASTOR-BEAN, RICINUS ZANZIBARENSIS

| Experiment | Sensitizing Dose | Second Dose | Result | Protection Test* |
|---|---|---|---|---|
| 1 | 0.01 gm. proteose, castor bean | 0.05 gm. proteose, castor bean | Died, 60 min. | |
| 2 | 0.01 gm. proteose, castor bean | 0.03 gm. proteose, castor bean | Died, 6 min. | |
| 3 | 0.01 gm. proteose, castor bean | 0.05 gm. globulin, castor bean | Doubtful.... | None; died in 1 hour |
| 4 | 0.01 gm. proteose, castor bean | 0.05 gm. globulin, castor bean | Doubtful.... | None; died in 20 minutes |
| 5 | 0.01 gm. globulin, castor bean | 0.05 gm. proteose, castor bean | Slight....... | None; severe reaction |
| 6 | 0.01 gm. globulin, castor bean | 0.05 gm. proteose, castor bean | Slight....... | None; severe reaction |
| 7 | 0.05 gm. proteose, castor bean | 0.05 gm. globulin, castor bean | 0 | None; died in 1 hour |

* The term "Protection Test" is applied to the reaction obtained after saturating the guinea-pig with the heterologous protein, and then injecting with the homologous protein. "None" means no protection, the animal still being strongly sensitive to the protein used for sensitizing.

The preparation of "proteose" used in these experiments was obtained in an extensive fractionation of the water-soluble proteins of the castor-bean, the purpose of which was to separate ricin in as pure a condition as possible. No evidence was obtained indicating enzymatic decomposition of the reserve protein in the extracts of this seed, and it is probable that the "proteose" was preformed in this seed. This preparation, which represents only a fraction of the total "proteose," was separated from the other proteins by dialyzing the sodium chlorid extract of the seed until all of the globulin had separated, and then subjecting the solution to fractional precipitation with alcohol. The extract was not heated during the process of isolation.

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[13] Jour. Infect. Dis., 1911, 8, p. 88.

These results are of interest as showing (a) the high anaphylactogenic power of the "proteose"; (b) the practically complete separation from ricin, for 50 milligrams, used for the sensitizing dose (Exper. 7), caused no symptoms of ricin poisoning, and 100 milligrams killed a guinea-pig weighing 400 grams only after ten days, whereas a preparation consisting chiefly of the albumin from the same extract which yielded this "proteose," killed rabbits in doses of 0.002 milligram per kilogram within three and one-half days; (c) the complete separation of globulin from the "proteose," for animals sensitized with even 50 milligrams gave no reaction when subsequently injected with the globulin; (d) evidence of a trace of "proteose" in the preparation of the globulin, for animals sensitized with 0.01 gm. of the globulin gave a slight reaction after a second dose of 0.05 gm. of "proteose." This trace of "proteose" was probably adsorbed during precipitation of the globulin, and doubtless could have been removed if the globulin had been reprecipitated several times.

TABLE 2
"Proteose," Flax-Seed, Linum Usitatissimum

| Experiment | Sensitizing Dose | Second Dose | Result | Protection Test |
|---|---|---|---|---|
| 1 | 0.01 gm. proteose, flax-seed | 0.10 gm. proteose, flax-seed | Died, 60 min. | |
| 2 | 0.005 gm. proteose, flax-seed | 0.10 gm. proteose, flax-seed | Severe, died during night | |
| 3 | 0.001 gm. proteose, flax-seed | 0.10 gm. proteose, brazil-nut | 0 | None; severe reaction |
| 4 | 0.001 gm. proteose, flax-seed | 0.05 gm. globulin, flax-seed | Slight....... | Partial; slight reaction |
| 5 | 0.005 gm. proteose, flax-seed | 0.05 gm. globulin, flax-seed | Moderate.... | Partial; slight reaction |
| 6 | 0.010 gm. globulin, flax-seed | 0.05 gm. proteose, flax-seed | Moderate.... | None; severe reaction |
| 7 | 0.010 gm. globulin, flax-seed | 0.05 gm. proteose, flax-seed | Slight, died during night | |
| 8 | 0.001 gm. globulin, flax-seed | 0.05 gm. proteose, flax-seed | Died, 1 hr. 30 min. | |
| 9 | 0.010 gm. proteose, flax-seed | 0.10 gm. proteose, hemp-seed | 0 | |

Whether this "proteose" is an original constituent of the seed, or a product of hydrolysis of the globulin is not known, but its anaphylactogenic activity indicates that it is not a hydrolytic product. That in this preparation the separation from the globulin was not complete is indicated by the slight to moderate reaction obtained when the globulin is administered to guinea-pigs sensitized with the "proteose." The presence of some "proteose" in the preparation of globulin is shown by the experiments made in the reverse order. Since the globulin was precipitated by dialysis from the extract containing the “proteose,” and as this preparation had not been especially purified by repeated precipitations, it is probable that a little “proteose” was adsorbed by the globulin during precipitation.

Unpublished experiments by one of us (O.) have made it very probable that a part, at least, of the “proteose” obtained from extracts of the hemp-seed is derived from edestin through changes that occur during the process of isolation. Under such circumstances edestin preparations might adsorb some of the proteose-like products which are formed. The slight reactions obtained between edestin and hemp-seed “proteose” may be thus explained. The much stronger reactions produced by sensitizing and intoxicating with the so-called proteose are doubtless caused by a protein distinctly different from edestin in chemical constitution rather than by the greater solubility of the “proteose” preparations in water.

TABLE 3
“Proteose,” Hemp-Seed, Cannabis Sativa

| Experiment | Sensitizing Dose | Second Dose | Result | Protection Test |
|---|---|---|---|---|
| 1 | 0.01 gm. proteose, hemp-seed | 0.05 gm. proteose, hemp-seed | Died, 30 min. | |
| 2 | 0.01 gm. proteose, hemp-seed | 0.10 gm. edestin, hemp-seed | Slight....... | None; severe reaction |
| 3 | 0.01 gm. proteose, hemp-seed | 0.10 gm. edestin, hemp-seed | Severe....... | Partial; moderate reaction |
| 4 | 0.01 gm. proteose, hemp-seed | 0.10 gm. edestin, hemp-seed | Slight....... | None; severe reaction |
| 5 | 0.01 gm. proteose, hemp-seed | 0.10 gm. edestin, hemp-seed | Slight....... | Partial; moderate reaction |
| 6 | 0.005 gm. proteose, hemp-seed | 0.10 gm. edestin, hemp-seed | 0 | Partial; slight reaction |
| 7 | 0.001 gm. proteose, hemp-seed | 0.10 gm. edestin, hemp-seed | 0 | Partial; slight reaction |
| 8 | 0.010 gm. edestin, hemp-seed | 0.05 gm. proteose, hemp-seed | Slight....... | None; moderate reaction |
| 9 | 0.010 gm. edestin, hemp-seed | 0.05 gm. proteose, hemp-seed | Slight....... | |
| 10 | 0.010 gm. proteose, hemp-seed | 0.05 gm. globulin, squash-seed | 0 | |

These experiments show that this preparation of proteose has been so completely separated from the globulin that its presence cannot be detected by this very delicate reaction, and that the “proteose” of the squash-seed is a distinctly different protein from the globulin. The moderate to doubtful reactions shown by guinea-pigs sensitized with the globulin and intoxicated with the “proteose” is to be ascribed to a natural toxicity of the “proteose” itself, demonstrated by control experiments, rather than to "proteose" adsorbed by the globulin during precipitation, for if the latter were the case some protection should have been afforded.

Excelsin separates from slightly acid solutions in beautiful hexagonal crystals, which are practically insoluble in pure water, but soluble in saline solutions. The crystals are compounds of excelsin with acid, i. e., a protein salt. If the acid is removed by being neutralized with alkali, excelsin is then soluble in pure water. Unless sufficient acid is present to convert all of the excelsin into the compound insoluble in water, more or less remains in solution when the salts are removed by dialysis. For this reason it is difficult to separate all of the excelsin from the "proteose." The results of these experiments indicate that this preparation of "proteose" contained some excelsin. The very great anaphylactic intoxicating power of the "proteose," shown by these experiments, demands a very complete separation of the "proteose" from the excelsin if no reaction is to be given by animals sensitized with excelsin and intoxicated by the "proteose." That this separation was not quite complete is shown by Experiments 11-19. Investigations of the proteins of the Brazil-nut indicate that this seed contains a relatively considerable quantity of preformed "proteose," and the results of the experiments here given show that this is biologically, and therefore chemically, distinct from excelsin.

TABLE 4
"PROTEOSE," SQUASH-SEED, CUCURBITA MAXIMA

| Experiment | Sensitizing Dose | Second Dose | Result | Protection Test |
|---|---|---|---|---|
| 1 | 0.01 gm. proteose, squash-seed | 0.05 gm. proteose, squash-seed | Died, 8 min. | |
| 2 | 0.01 gm. proteose, squash-seed | 0.05 gm. proteose, castor bean | 0 | |
| 3 | 0.01 gm. proteose, squash-seed | 0.05 gm. globulin, squash-seed | 0 | None; severe reaction |
| 4 | 0.01 gm. proteose, squash-seed | 0.05 gm. globulin, squash-seed | 0 | None; died |
| 5 | 0.001 gm. proteose, squash-seed | 0.05 gm. globulin, squash-seed | 0 | |
| 6 | 0.001 gm. proteose, squash-seed | 0.05 gm. globulin, squash-seed | 0 | None; severe reaction |
| 7 | 0.010 gm. globulin, squash-seed | 0.05 gm. proteose, squash-seed | Moderate.... | None; severe reaction |
| 8 | 0.010 gm. globulin, squash-seed | 0.05 gm. proteose, squash-seed | Moderate.... | None; severe reaction |
| 9 | 0.001 gm. globulin, squash-seed | 0.05 gm. proteose, squash-seed | Doubtful.... | None; died |
| 10 | 0.001 gm. globulin, squash-seed | 0.05 gm. proteose, squash-seed | Doubtful.... | None; died |

On account of the evident admixture of excelsin with our preparation of "Brazil-nut proteose," an attempt was made to purify it further.

Six grams were shaken thoroughly with distilled water and filtered after standing twelve hours on ice. A perfectly clear filtrate was obtained, and about 2 gm. of insoluble residue were left undissolved. The protein in the filtrate was precipitated with alcohol, and dried with alcohol and ether, about 4 gm. of material being obtained. Two guinea-pigs sensitized with excelsin were given each 0.05 gm. of this preparation; one died in twenty-eight minutes, the other nearly died. Two guinea-pigs sensitized with 0.001 gm. of this "proteose" reacted severely to 0.05 gm. excelsin, one dying in the night. The minimal lethal dose of this preparation for 300 gm. guinea-pigs sensitized with it was between 0.001 gm. and 0.002 gm. Since this preparation evidently still contained excelsin, the process was repeated four times more, using only about 50 to 100 c.c. water for each re-solution. Each time there was some material that dissolved only slowly in water, and this was discarded as far as possible. Finally about 0.5 gm. of material was left which was readily soluble in 50 c.c. of water, but even this preparation sensitized fatally to excelsin, and caused severe reactions in guinea-pigs sensitized with excelsin. These experiments show that it is very difficult, if not impossible, to separate excelsin and "proteose" completely.

TABLE 5

"Proteose," Brazil-Nut, Bertholletia Excelsa

| Experiment | Sensitizing Dose | Second Dose | Result | Protection Test |
|---|---|---|---|---|
| 1 | 0.01 gm. proteose, brazil-nut | 0.10 gm. proteose, brazil-nut | Died, 15 min. | |
| 2 | 0.0005 gm. proteose, brazil-nut | 0.10 gm. proteose, brazil-nut | Died, 20 min. | |
| 3 | 0.002 gm. proteose, brazil-nut | 0.10 gm. proteose, flax-seed | 0 | None; died, 8 minutes |
| 4 | 0.001 gm. proteose, brazil-nut | 0.10 gm. proteose, flax-seed | 0 | None; died, 8 minutes |
| 5 | 0.001 gm. proteose, brazil-nut | 0.001 gm. proteose, brazil-nut | Died, 12 min. | |
| 6 | 0.001 gm. proteose, brazil-nut | 0.002 gm. proteose, brazil-nut | Died, 12 min. | |
| 7 | 0.001 gm. proteose, brazil-nut | 0.0005 gm. proteose, brazil-nut | Died, 80 min. | |
| 8 | 0.001 gm. proteose, brazil-nut | 0.0005 gm. proteose, brazil-nut | Died, 70 min. | |
| 9 | 0.001 gm. proteose, brazil-nut | 0.0001 gm. proteose, brazil-nut | Severe | |
| 10 | 0.001 gm. proteose, brazil-nut | 0.00005 gm. proteose, brazil-nut | Slight....... | Killed by 0.05 gm. excelsin |
| 11 | 0.005 gm. proteose, brazil-nut | 0.05 gm. excelsin, brazil-nut | Severe....... | Nearly complete; slight reaction |
| 12 | 0.001 gm. proteose, brazil-nut | 0.05 gm. excelsin, brazil-nut | Severe....... | Nearly complete; slight reaction |
| 13 | 0.0005 gm. proteose, brazil-nut | 0.05 gm. excelsin, brazil-nut | Severe, died in night | |
| 14 | 0.05 gm. proteose, brazil-nut | 0.10 gm. excelsin, brazil-nut | Died, 1 hr. | |
| 15 | 0.001 gm. proteose, brazil-nut | 0.10 gm. excelsin, brazil-nut | Died, 45 min. | |
| 16 | 0.01 gm. excelsin, brazil-nut | 0.05 gm. proteose, brazil-nut | Slight....... | Partial; moderate reaction |
| 17 | 0.01 gm. excelsin, brazil-nut | 0.05 gm. proteose, brazil-nut | Slight....... | Partial; moderate reaction |
| 18 | 0.001 gm. excelsin, brazil-nut | 0.05 gm. proteose, brazil-nut | Died, 6 min. | |
| 19 | 0.001 gm. excelsin, brazil-nut | 0.05 gm. proteose, brazil-nut | Severe | |

A series of experiments was also performed in which the effect of heating the unpurified Brazil-nut "proteose" was examined. The "proteose" was suspended in water and heated one-half hour at 100 C.; after the suspension had cooled, sodium hydrate was added to make 0.1 percent, but the "proteose" did not completely dissolve. It was found that with this heated "proteose" fatal results were produced in sensitized guinea-pigs with doses of 0.002 to 0.005 gm., and, of two guinea-pigs given 0.001 gm., one died after several hours, while the other was only moderately intoxicated; 0.0005 gm. doses caused but slight to moderate symptoms. As 0.0005 gm. doses of the unheated "proteose" were found regularly fatal, it is evident that heating does somewhat impair the anaphylactic toxicity of this "proteose," altho the effect of heat is relatively slight, as compared with the effect of heat on coagulable proteins, and may well be ascribed to the coagulation of the excelsin present in this preparation.

TABLE 6
"PROTEOSE," BLACK-WALNUT, JUGLANS NIGRA

| Experiment | Sensitizing Dose | Second Dose | Result |
|---|---|---|---|
| 1 | 0.01 gm. proteose, walnut...... | 0.05 gm. proteose, walnut...... | Died, 45 minutes |
| 2 | 0.01 gm. proteose, walnut...... | 0.05 gm. proteose, walnut...... | Severe reaction |
| 3 | 0.01 gm. proteose, walnut...... | 0.05 gm. globulin, walnut...... | Severe reaction |
| 4 | 0.01 gm. proteose, walnut...... | 0.05 gm. globulin, walnut...... | Died, 90 minutes |
| 5 | 0.01 gm. globulin, walnut...... | 0.05 gm. proteose, walnut...... | Severe reaction |
| 6 | 0.01 gm. globulin, walnut...... | 0.05 gm. proteose, walnut...... | Severe reaction |

TABLE 7
"PROTEOSE," HAZEL-NUT, CORYLUS AVELLENA

| Experiment | Sensitizing Dose | Second Dose | Result | Protection Test |
|---|---|---|---|---|
| 1 | 0.005 gm. proteose, hazel-nut | 0.05 gm. proteose, hazel-nut | Died, 15 min. | |
| 2 | 0.005 gm. proteose, hazel-nut | 0.05 gm. proteose, lentil | 0 | None; severe reaction |
| 3 | 0.005 gm. proteose, hazel-nut | 0.05 gm. proteose, lentil | 0 | Partial; moderate reaction |
| 4 | 0.010 gm. proteose, hazel-nut | 0.05 gm. corylin, hazel-nut | Severe....... | None; severe reaction |
| 5 | 0.010 gm. proteose, hazel-nut | 0.05 gm. corylin, hazel-nut | Died, 30 min. | |
| 6 | 0.010 gm. corylin, hazel-nut | 0.05 gm. proteose, hazel-nut | Doubtful.... | Complete; no reaction |
| 7 | 0.010 gm. corylin, hazel-nut | 0.05 gm. proteose, hazel-nut | Slight....... | Complete; slight reaction |
| 8 | 0.001 gm. proteose, hazel-nut | 0.001 gm. proteose, hazel-nut | Slight | |
| 9 | 0.001 gm. proteose, hazel-nut | 0.002 gm. proteose, hazel-nut | Slight | |
| 10 | 0.001 gm. proteose, hazel-nut | 0.003 gm. proteose, hazel-nut | Slight | |
| 11 | 0.001 gm. proteose, hazel-nut | 0.004 gm. proteose, hazel-nut | Severe, died in night | |

As previously mentioned, juglansin, the globulin found in different species of walnuts, separates on dialyzing the sodium chlorid extract of the seed only when this contains a certain small proportion of acid. For this reason it is very difficult to obtain from this seed preparations of "proteose" which are free from globulin. The preparation used for these experiments evidently contained a relatively large amount of the globulin.

This preparation of "proteose" from the hazel-nut, which apparently has less anaphylactogenic power than the natural "proteose" of the Brazil-nut, evidently contained enough of the globulin, corylin, to sensitize the animals to corylin, but not enough to intoxicate animals sensitized with corylin. The preparation of corylin appears, therefore, to be nearly free from "proteose," but the "proteose" is not free from corylin. The imperfect separation of corylin from the "proteose" can be attributed to the same cause as that assigned to the incomplete separation of excelsin or juglansin from the "proteoses" of the Brazil-nut and walnut, respectively. These experiments show that corylin is chemically distinct from the "proteose."

TABLE 8
"PROTEOSE" AND "PROTOPROTEOSE," PEA, PISUM SATIVUM

| Experiment | Sensitizing Dose | Second Dose | Result | Protection Test |
|---|---|---|---|---|
| 1 | 0.01 gm. proteose, pea | 0.05 gm. proteose, pea | Severe....... | Nearly complete |
| 2 | 0.01 gm. proteose, pea | 0.04 gm. protoproteose, pea | Severe....... | Nearly complete |
| 3 | 0.01 gm. proteose, pea | 0.10 gm. legumin, pea | Slight....... | Slight or none |
| 4 | 0.01 gm. proteose, pea | 0.10 gm. legumin, pea | Slight....... | Slight or none |
| 5 | 0.01 gm. protoproteose, pea | 0.05 gm. proteose, pea | Severe....... | Partial |
| 6 | 0.01 gm. protoproteose, pea | 0.05 gm. protoproteose, pea | Died, 3 min. | |
| 7 | 0.01 gm. protoproteose, pea | 0.05 gm. proteose, pea | Severe....... | Partial |
| 8 | 0.01 gm. protoproteose, pea | 0.10 gm. legumin, pea | Doubtful.... | Partial |
| 9 | 0.01 gm. vicilin, pea | 0.05 gm. proteose, pea | Doubtful.... | Partial |
| 10 | 0.01 gm. vicilin, pea | 0.05 gm. proteose, pea | 0 | Partial |
| 11 | 0.01 gm. vicilin, pea | 0.05 gm. protoproteose, pea | Moderate.... | Partial |
| 12 | 0.01 gm. legumin, pea | 0.05 gm. proteose, pea | 0 | Partial |
| 13 | 0.01 gm. legumin, pea | 0.05 gm. proteose, pea | Doubtful.... | Partial |
| 14 | 0.01 gm. legumin, pea | 0.05 gm. protoproteose, pea | Slight....... | Partial |
| 15 | 0.01 gm. legumin, pea | 0.05 gm. protoproteose, pea | Moderate.... | Partial |

The preparation of "protoproteose" was made by the conventional methods formerly used in separating mixtures of proteoses into fractions, to which distinguishing names have been assigned, e. g., proto-, deutero-, etc., proteose. Thus, the total protein extracted from the seed was precipitated by saturating with ammonium sulphate, the solution of the precipitate freed from globulin by long dialysis, the albumins separated from the filtrate by heating to 95 C., and the total "proteose" then remaining in solution precipitated by dialyzing its solution into large quantities of alcohol. By dissolving this precipitate in distilled water, and again dialyzing its clear solution into alcohol, the preparation here called "proteose" was obtained. The "protoproteose" was made by dissolving the "proteose" in ten times its weight of water, saturating the solution with sodium chlorid, and adding dilute acetic acid, saturated with sodium chlorid, as long as a precipitate was formed. The resulting precipitate was then washed with a saturated sodium chlorid solution, dissolved in water, and the solution dialyzed in water until free from chlorin. By then dialyzing the solution into alcohol the "protoproteose" was precipitated, and after being washed with absolute alcohol and dried over sulphuric acid it yielded the preparation used for these experiments.

The results here recorded are of interest as they show it to be possible to separate several proteins from each other, even when present in the same extract. They also show that the products thus separated are chemically distinct from one another. According to previous investigations the pea contains two globulins, legumin and vicilin; an albumin, legumelin; and one or more "proteoses." The reactions given in Table 8 show that the "proteose" not only has been very completely separated from legumin and vicilin, but that it is a chemically distinct protein. The reactions between the preparation designated "protoproteose" and that designated "proteose" give no evidence of more than one substance in the total "proteose."

TABLE 9
"Proteose," Lentil, Ervum Lens

| Experiment | Sensitizing Dose | Second Dose | Result | Protection Test |
|---|---|---|---|---|
| 1 | 0.005 gm. proteose, lentil | 0.05 gm. proteose, lentil | Severe....... | Complete |
| 2 | 0.005 gm. proteose, lentil | 0.05 gm. proteose, lentil | Died, 1 hr. | |
| 3 | 0.005 gm. proteose, lentil | 0.05 gm. corylin, hazel-nut | 0 | None |
| 4 | 0.005 gm. proteose, lentil | 0.05 gm. corylin, hazel-nut | 0 | None |
| 5 | 0.001 gm. proteose, lentil | 0.05 gm. legumin, lentil | 0 | None |
| 6 | 0.001 gm. proteose, lentil | 0.05 gm. legumin, lentil | 0 | None |
| 7 | 0.001 gm. proteose, lentil | 0.05 gm. legumin, lentil | 0 | None |
| 8 | 0.001 gm. proteose, lentil | 0.05 gm. legumin, lentil | 0 | None |
| 9 | 0.001 gm. legumin, lentil | 0.05 gm. proteose, lentil | 0 | None |
| 10 | 0.001 gm. legumin, lentil | 0.05 gm. proteose, lentil | 0 | None |
| 11 | 0.001 gm. proteose, soy-bean | 0.05 gm. proteose, lentil | Doubtful.... | None |
| 12 | 0.001 gm. proteose, soy-bean | 0.05 gm. proteose, lentil | Doubtful.... | None |
| 13 | 0.005 gm. proteose, kidney-bean | 0.05 gm. proteose, lentil | Slight....... | None |
| 14 | 0.005 gm. proteose, kidney-bean | 0.05 gm. proteose, lentil | Slight....... | None |

The preparation of "proteose" from the lentil used for these experiments was made in the same way as the "proteose" preparation from the pea (see under Table 8).

The results show that the separation of legumin and "proteose" was very complete, and that the latter is a chemically distinct protein. Lentil proteose is also quite distinct from the "proteose" of the soy bean (Glycine hispida), and the proteose of the kidney bean (Phaseolus vulgaris). (This preparation of "proteose" from the kidney bean was too toxic for normal guinea-pigs, which it killed in eight to sixteen hours in 0.05 gm. doses, to be used for anaphylaxis experiments except in small doses for sensitization.[14])

TABLE 10

"PROTEOSE," SOY-BEAN, GLYCINE HISPIDA

| Experiment | Sensitizing Dose | Second Dose | Result | Protection Test |
|---|---|---|---|---|
| 1 | 0.01 gm. proteose, soy-bean | 0.05 gm. proteose, soy-bean | Died, 15 min. | |
| 2 | 0.01 gm. proteose, soy-bean | 0.05 gm. proteose, soy-bean | Died, 60 min. | |
| 3 | 0.001 gm. proteose, soy-bean | 0.002 gm. proteose, soy-bean | Died, 2 hr. | |
| 4 | 0.001 gm. proteose, soy-bean | 0.001 gm. proteose, soy-bean | Severe | |
| 5 | 0.001 gm. proteose, soy-bean | 0.0005 gm. proteose, soy-bean | Moderate | |
| 6 | 0.001 gm. proteose, soy-bean | 0.0001 gm. proteose, soy-bean | Moderate | |
| 7 | 0.001 gm. proteose, soy-bean | 0.0001 gm. proteose, soy-bean | Moderate | |
| 8 | 0.001 gm. proteose, soy-bean | 0.00005 gm. proteose, soy-bean | Slight | |
| 9 | 0.001 gm. proteose, soy-bean | 0.00001 gm. proteose, soy-bean | Doubtful | |
| 10 | 0.01 gm. proteose, soy-bean | 0.10 gm. glycinin, soy-bean | Slight....... | Partial |
| 11 | 0.01 gm. proteose, soy-bean | 0.10 gm. glycinin, soy-bean | Slight....... | Partial |
| 12 | 0.01 gm. glycinin, soy-bean | 0.05 gm. proteose, soy-bean | Severe....... | Partial |
| 13 | 0.01 gm. glycinin, soy-bean | 0.05 gm. proteose, soy-bean | Moderate.... | Partial |
| 14 | 0.001 gm. proteose, soy-bean | 0.05 gm. proteose, lentil | Doubtful.... | None |
| 15 | 0.001 gm. proteose, soy-bean | 0.05 gm. proteose, lentil | Doubtful.... | None |
| 16 | 0.001 gm. proteose, soy-bean | 0.05 gm. proteose, pea | Moderate.... | None |
| 17 | 0.001 gm. proteose, soy-bean | 0.05 gm. proteose, pea | Slight....... | None |
| 18 | 0.005 gm. proteose, pea | 0.05 gm. proteose, soy-bean | Slight....... | None |

From the foregoing data it is plain that the soy-bean "proteose" is chemically distinct from glycinin and exhibits strong anaphylactogenic properties. The preparation of proteose appears to be free from glycinin, but the glycinin contains enough proteose to sensitize, altho only enough to produce slight intoxication.

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[14] Schneider, Jour. Biol. Chem., 1912, 11, p. 47.

Experiments 14, 15, and 16 show that the preparation of globulin was free from "proteose," and, in conjunction with Experiments 1 and 13, that these are distinctly different substances. Experiments 10, 11, and 12 indicate that this preparation of "proteose" contained enough globulin to sensitize the animals strongly.

TABLE 11

"Proteose," Adzuki-Bean, Phaseolus Radiatus

| Experiment | Sensitizing Dose | Second Dose | Result | Protection Test |
|---|---|---|---|---|
| 1 | 0.01 gm. proteose, adzuki-bean | 0.05 gm. proteose, adzuki-bean | Died, 45 min. | |
| 2 | 0.001 gm. proteose, adzuki-bean | 0.001 gm. proteose, adzuki-bean | Died, 55 min. | |
| 3 | 0.001 gm. proteose, adzuki-bean | 0.0005 gm. proteose, adzuki-bean | Slight | |
| 4 | 0.001 gm. proteose, adzuki-bean | 0.0002 gm. proteose, adzuki-bean | Slight | |
| 5 | 0.001 gm. proteose, adzuki-bean | 0.0001 gm. proteose, adzuki-bean | Doubtful | |
| 6 | 0.001 gm. proteose, adzuki-bean | 0.05 gm. proteose, lentil | 0 | Partial; moderate reaction |
| 7 | 0.001 gm. proteose, adzuki-bean | 0.05 gm. proteose, lentil | 0 | Partial; moderate reaction |
| 8 | 0.001 gm. proteose, adzuki-bean | 0.05 gm. proteose, pea | 0 | Partial; moderate reaction |
| 9 | 0.001 gm. proteose, adzuki-bean | 0.05 gm. proteose, pea | 0 | Partial; moderate reaction |
| 10 | 0.01 gm. proteose, adzuki-bean | 0.05 gm. globulin, adzuki-bean | Slight....... | Partial; moderate reaction |
| 11 | 0.01 gm. proteose, adzuki-bean | 0.05 gm. globulin, adzuki-bean | Died, 30 min. | |
| 12 | 0.01 gm. proteose, adzuki-bean | 0.05 gm. globulin, adzuki-bean | Moderate.... | Partial; moderate reaction |
| 13 | 0.01 gm. globulin, adzuki-bean | 0.05 gm. globulin, adzuki-bean | Died, 20 min. | |
| 14 | 0.01 gm. globulin, adzuki-bean | 0.05 gm. proteose, adzuki-bean | 0 | Partial; moderate reaction |
| 15 | 0.01 gm. globulin, adzuki-bean | 0.05 gm. proteose, adzuki-bean | 0 | Partial; moderate reaction |
| 16 | 0.01 gm. globulin, adzuki-bean | 0.05 gm. proteose, adzuki-bean | Slight....... | Partial; moderate reaction |

Having found that the so-called proteose obtained from extracts of the hemp-seed has high anaphylactogenic power, we have tested the artificial proteoses made from edestin by hydrolyzing with 2 percent sulphuric acid, and also by heating with water under pressure. We have also tested the anaphylactogenic power of a preparation of proteose made by hydrolyzing zein with 2 percent sulphuric acid. For these valuable preparations we are indebted to Prof. F. P. Underhill. The outcome of these experiments is given in the following tables.

The slight reaction shown by animals sensitized with 0.01 gm. of these artificial proteoses when injected with 0.10 gm. of the same, can as well be ascribed to an incomplete separation of edestin from the preparation used as to feeble anaphylactogenic power of these artificial proteoses themselves. This assumption is made probable by other experiments which strongly indicate the presence of enough edestin in the preparations of proteose highly to sensitize the animals to edestin (Experiments 3, 4, 17, and 18), but not enough to intoxicate animals sensitized with edestin (Experiments 9 and 10). Experiments 5, 6, 7, 8, 13, and 14 show that the natural proteose of the hemp-seed is chemically distinct from these artificial derivatives of edestin.

TABLE 12

Artificial Proteose, Made From Edestin by Hydrolysis With 2 Percent $H_2SO_4$

| Experiment | Sensitizing Dose | Second Dose | Result | Protection Test |
|---|---|---|---|---|
| 1 | 0.01 gm. proteose, edestin | 0.10 gm. proteose, edestin | Slight....... | Still reacts to edestin |
| 2 | 0.01 gm. proteose, edestin | 0.10 gm. proteose, edestin | Slight....... | Still reacts to edestin |
| 3 | 0.01 gm. proteose, edestin | 0.10 gm. edestin, hemp-seed | Died, 60 min. | |
| 4 | 0.01 gm. proteose, edestin | 0.10 gm. edestin, hemp-seed | Severe....... | Complete. No reaction to edestin |
| 5 | 0.01 gm. proteose, edestin | 0.05 gm. proteose, hemp-seed | 0 | No reaction to edestin proteose |
| 6 | 0.01 gm. proteose, edestin | 0.05 gm. proteose, hemp-seed | 0 | No reaction to edestin proteose |
| 7 | 0.01 gm. proteose, edestin | 0.10 gm. proteose, hemp-seed | Doubtful.... | Severe reaction to edestin |
| 8 | 0.01 gm. proteose, edestin | 0.10 gm. proteose, hemp-seed | 0 | Severe reaction to edestin |
| 9 | 0.01 gm. edestin, hemp-seed | 0.10 gm. proteose, edestin | Slight....... | Slight reaction to edestin |
| 10 | 0.01 gm. edestin, hemp-seed | 0.10 gm. proteose, edestin | Slight....... | Slight reaction to edestin |
| Artificial Proteose Made From Edestin by Hydrolysis With $H_2O$ in Autoclave | | | | |
| 11 | 0.01 gm. proteose, edestin | 0.10 gm. proteose, edestin | Slight...... | Still reacts to edestin |
| 12 | 0.01 gm. proteose, edestin | 0.10 gm. proteose, edestin | Slight....... | Still reacts to edestin |
| 13 | 0.01 gm. proteose, edestin | 0.10 gm. proteose, hemp-seed | 0 | Still reacts to edestin |
| 14 | 0.01 gm. proteose, edestin | 0.10 gm. proteose, hemp-seed | 0 | Still reacts to edestin |
| 15 | 0.01 gm. proteose, edestin | 0.10 gm. edestin, hemp-seed | Doubtful.... | Does not react to edestin |
| 16 | 0.01 gm. proteose, edestin | 0.10 gm. edestin, hemp-seed | Doubtful.... | Does not react to edestin |
| 17 | 0.01 gm. proteose, edestin | 0.10 gm. edestin, hemp-seed | Severe | |
| 18 | 0.01 gm. proteose, edestin | 0.10 gm. edestin, hemp-seed | Died | |

This artificial zein proteose, made by acid hydrolysis of zein, is entirely inert, both as regards sensitizing and intoxicating properties, in contrast with the natural "proteoses" of seeds.

Two preparations of artificial zeose made by B. M. Hendrix were also tested, and found not to cause any reactions whatever, or to sensitize to zein. These proteoses were prepared as follows:

The zein was suspended in 0.2 percent hydrochloric acid and some Parke-Davis pepsin added to the solution; the mixture was placed in an incubator at 37 C. and allowed to digest for two days. It was then filtered and the insoluble material was treated as before for two days. This was continued until practically all went into solution. The filtrate was neutralized and filtered and then saturated with ammonium sulphate. The zeose which was thus precipitated was then dissolved in a small quantity of water, dialyzed until free from ammonium sulphate, and its solution evaporated to dryness.

Since both zein and edestin, the proteins from which our artificial proteoses were prepared, are relatively inactive in anaphylactic reactions,[15] proteoses were prepared from squash seed globulin (for this preparation of globulin we are indebted to Dr. Isaac F. Harris), which is one of the most active anaphylactogens of all the vegetable proteins that we have studied.

TABLE 13

ARTIFICIAL PROTEOSE MADE FROM ZEIN BY HYDROLYSIS WITH $H_2SO_4$

| Experiment | Sensitizing Dose | Second Dose | Result |
|---|---|---|---|
| 1 | 0.01 gm. proteose, zein............ | 0.10 gm. proteose, zein............ | None |
| 2 | 0.01 gm. proteose, zein............ | 0.05 gm. proteose, zein............ | None |
| 3 | 0.01 gm. proteose, zein............ | 0.05 gm. proteose, zein............ | None |
| 4 | 0.01 gm. proteose, zein............ | 0.05 gm. zein...................... | None |
| 5 | 0.01 gm. proteose, zein............ | 0.05 gm. zein...................... | None |
| 6 | 0.01 gm. proteose, zein............ | 0.05 gm. zein...................... | None |
| 7 | 0.01 gm. proteose, zein............ | 0.05 gm. zein...................... | None |
| 8 | 0.01 gm. zein...................... | 0.10 gm. proteose, zein............ | None |

The proteoses were prepared by digesting with pepsin-HCl until but a small amount of globulin could be precipitated by one-third saturation with ammonium sulphate. After removal of the globulin, two preparations of proteose were made, one containing all the material precipitated between half saturation and full saturation, therefore consisting chiefly of "deutero" proteoses (Preparation 1), and the other containing the precipitate coming down between one-third and full saturation, therefore presumably containing both "primary" and "deutero" proteoses (Preparation 2).

The results of experiments with these preparations were as follows:

According to the results of these experiments, it would seem that our Preparation 1 of proteose from the squash-seed globulin contains traces of globulin sufficient to sensitize to the latter, but not sufficient

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15. Jour. Infect. Dis., 1911, 8, p. 88.

to intoxicate sensitized guinea-pigs. Proteose 1 itself causes only slight effects when given in doses of 50 milligrams to sensitized animals. It is thus evident that this typical proteose, prepared by peptic digestion, is entirely different from the so-called proteoses found preformed in seeds. Proteose 2 shows more activity than Proteose 1, which contains the fraction precipitated between half and full saturation with $(NH_4)_2SO_4$, possibly because it contains sufficient unaltered globulin to produce some reaction, even when used as the intoxicating dose.

TABLE 14

ARTIFICIAL PROTEOSE MADE FROM SQUASH-SEED GLOBULIN BY PEPSIN

| Experiment | Sensitizing Dose | Second Dose | Result | tection Test |
|---|---|---|---|---|
| 1 | 0.003 gm. Proteose 1, squash-seed globulin | 0.05 gm. Proteose 1, squash-seed globulin | Slight | |
| 2 | 0.003 gm. Proteose 1, squash-seed globulin | 0.05 gm. Proteose 1, squash-seed globulin | Moderate | |
| 3 | 0.003 gm. Proteose 1, squash-seed globulin | 0.05 gm. globulin, squash-seed | Died, 1 hr. 40 min. | |
| 4 | 0.003 gm. Proteose 1, squash-seed globulin | 0.05 gm. globulin, squash-seed | Moderate | |
| 5 | 0.003 gm. globulin, squash-seed | 0.05 gm. Proteose 1, squash-seed globulin | 0 | Partial |
| 6 | 0.003 gm. globulin, squash-seed | 0.05 gm. Proteose 1, squash-seed globulin | 0 | Partial |
| 7 | 0.005 gm. Proteose 2, squash-seed globulin | 0.05 gm. Proteose 2, squash-seed globulin | Moderate | |
| 8 | 0.005 gm. Proteose 2, squash-seed globulin | 0.05 gm. Proteose 2, squash-seed globulin | Moderate | |
| 9 | 0.005 gm. Proteose 2, squash-seed globulin | 0.05 gm. Proteose 2, squash-seed globulin | Doubtful | |
| 10 | 0.005 gm. Proteose 2, squash-seed globulin | 0.05 gm. Proteose 2, squash-seed globulin | Doubtful | |
| 11 | 0.005 gm. Proteose 2, squash-seed globulin | 0.05 gm. Proteose 2, squash-seed globulin | Died, 95 min. | |
| 12 | 0.005 gm. Proteose 2, squash-seed globulin | 0.05 gm. globulin, squash-seed | Died, 50 min. | |
| 13 | 0.005 gm. Proteose 2, squash-seed globulin | 0.05 gm. globulin, squash-seed | Died, 40 min. | |
| 14 | 0.005 gm. Proteose 2, squash-seed globulin | 0.05 gm. globulin, squash-seed | Died, 40 min. | |
| 15 | 0.005 gm. Proteose 2, squash-seed globulin | 0.05 gm. globulin, squash-seed | Severe...... | Complete |
| 16 | 0.005 gm. globulin, squash-seed | 0.05 gm. Proteose 2, squash-seed globulin | Died, 25 min. | |
| 17 | 0.005 gm. globulin, squash-seed | 0.05 gm. Proteose 2, squash-seed globulin | Died, 25 min. | |
| 18 | 0.005 gm. globulin, squash-seed | 0.05 gm. Proteose 2, squash-seed globulin | Moderate... | Partial |
| 19 | 0.005 gm. globulin, squash-seed | 0.05 gm. Proteose 2, squash-seed globulin | Moderate... | Partial |

## SUMMARY

The reaction of anaphylaxis demonstrates that those vegetable protein preparations, commonly designated "proteoses" because their solubility is like that of the proteoses produced by the action of pepsin or trypsin on native proteins, are distinguishable by biologic reactions and

therefore are chemically distinct from the other reserve proteins of the seeds. The "proteoses" obtained from different seeds and grains are also quite distinct from one another.

They exhibit strong anaphylactogenic properties and cause very severe anaphylactic intoxication when injected into sensitized guinea-pigs, even in minute doses (.001 to .0005 gm. being fatal doses with some of them). Their activity in this respect resembles that of the soluble animal proteins, such as egg-white, serum, etc., and greatly exceeds that of any of the other vegetable proteins (globulins, alcohol-soluble proteins, etc.) which we have studied. This high anaphylactic activity seems to depend upon their great solubility in the body fluids, as shown in Paper V of this series.[16] Their activity is not destroyed by heating at 100 C. for one-half hour, presumably because of their incoagulability.

In their anaphylactic power these "natural proteoses" differ sharply from proteoses obtained from animal proteins by digestion with enzymes, or by chemical hydrolysis, such artificial products being almost, if not entirely, non-anaphylactogenic. Furthermore, those products of hydrolysis which result from heating vegetable proteins with acids, with water under pressure, or by peptic digestion, have, so far as we have tested them, no anaphylactogenic properties. From these facts it would seem that the vegetable "proteoses" belong to a group of proteins which are chemically different from any heretofore recognized. They resemble highly soluble native proteins in their anaphylactogenic capacity, and are probably quite as complex in their chemical constitution. Their designation as "proteoses" is consequently improper.

This differentiation of so many of these "proteose" preparations from the other proteins in the same seed is a striking example of the fact that "specificity of the anaphylaxis reaction is not dependent on biologic origin, but on chemical constitution." Our experiments show also that these soluble proteins, which occur in the seeds of so many species of plants, are as distinct from one another as are the other more abundant proteins.

The results described in this paper demonstrate that anaphylaxis furnishes a useful means for determining the purity of protein preparations obtained from plant extracts, in so far as contamination with the other proteins of the same seed is concerned.

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[16] Jour. Infect. Dis., 1914, 14, p. 377.